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Inhibition of Interleukin-1 by Anakinra Improves Vascular and Left Ventricular Function in Patients With Rheumatoid Arthritis

Ignatios Ikonomidis, MD; John P. Lekakis, MD; Maria Nikolaou, MD; Ioannis Paraskevaidis, MD; Ioanna Andreadou, PhD; Theophania Kaplanoglou, MD; Pelagia Katsimbri, MD; Grigorios Skarantavos, MD; Panayiotis N. Soucacos, MD; Dimitrios T. Kremastinos, MD

Background—Interleukin-1 increases nitrooxidative stress. We investigated the effects of a human recombinant interleukin-1a receptor antagonist (anakinra) on nitrooxidative stress and vascular and left ventricular function.

Methods and Results—In an acute, double-blind trial, 23 patients with rheumatoid arthritis were randomized to receive a single injection of anakinra (150 mg SC) or placebo and, after 48 hours, the alternative treatment. At baseline and 3 hours after the injection, we assessed (1) coronary flow reserve, aortic distensibility, systolic and diastolic (Em) velocity of the mitral annulus, and E to Em ratio (E/Em) using echocardiography; (2) flow-mediated, endothelium-dependent dilation of the brachial artery; and (3) malondialdehyde, nitrotyrosine, interleukin-6, endothelin-1, and C-reactive protein. In a chronic, nonrandomized trial, 23 patients received anakinra and 19 received prednisolone for 30 days, after which all indices were reassessed. Compared with baseline, there was a greater reduction in malondialdehyde, nitrotyrosine, interleukin-6, and endothelin-1 and a greater increase in flow-mediated dilation, coronary flow reserve, aortic distensibility, systolic velocity of mitral annulus, and E/Em after anakinra than after placebo (malondialdehyde -25% versus 9% ; nitrotyrosine -38% versus -11% ; interleukin-6 -29% versus 0.9% ; endothelin-1 -36% versus -11% ; flow-mediated dilation 45% versus -9% ; coronary flow reserve 29% versus 4% ; and aortic distensibility 45% versus 2% ; $P < 0.05$ for all comparisons). After 30 days of treatment, the improvement in biomarkers and in vascular and left ventricular function was greater in the anakinra group than in the prednisolone group ($P < 0.05$).

Conclusions—Interleukin-1 inhibition improves vascular and left ventricular function and is associated with reduction of nitrooxidative stress and endothelin. (*Circulation*. 2008;117:2662-2669.)

Key Words: interleukins ■ inflammation ■ endothelium ■ inhibitors ■ microcirculation

Atherogenesis shares similar pathophysiological mechanisms with the inflammatory process in patients with rheumatoid arthritis (RA),¹ such as increased oxidative² and nitrosative³ stress and production of interleukin-1 (IL-1), interleukin-6 (IL-6),⁴⁻⁶ and endothelin.⁷ IL-1 enhances the production of IL-6, C-reactive protein (CRP),⁴⁻⁶ and endothelin-1 (ET-1)⁸ and promotes the release of superoxide anion.⁹ IL-1 also causes the excess release of NO⁻,¹⁰ which reacts with the superoxide anion to form the peroxynitrite.¹¹ This molecule causes nitration of tyrosine, which leads to generation of nitrotyrosine, a marker of nitrosative stress.^{3,11} Nitrooxidative stress contributes to endothelial dysfunction¹² and abnormal coronary vasoreactivity in experimental models.¹³ IL-1 may impair coronary microcirculation and myocardial function through production of ET-1,¹⁴ peroxynitrite,¹⁵ and/or IL-6, a cytokine with negative inotropic action.^{6,16,17} Treatment with the IL-1 receptor antagonist (IL-1ra) reduces IL-1-mediated oxidative tissue damage.¹⁸

Anakinra, a recombinant form of human IL-1ra, is used for the treatment of RA.^{19,20}

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Endothelial dysfunction may impair coronary flow reserve (CFR)²¹⁻²³ and aortic function.²⁴ Reduction of oxidative stress improves endothelial function²⁵ and CFR within 3 hours.²¹⁻²³ Thus, we hypothesized that inhibition of IL-1 would reduce nitrooxidative stress, leading to a rapid improvement in vascular and LV function.

In the present study, we investigated the acute and chronic effects of anakinra on endothelial function (as assessed by flow-mediated dilation [FMD] of the brachial artery²⁶), CFR and left ventricular (LV) function (as assessed by transthoracic Doppler and tissue Doppler echocardiography,^{27,28} respectively), and arterial function (as assessed by aortic root echocardiography²⁹ and pulse-wave velocity [PWV]³⁰) in RA

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Table 1. Study Cohort

	Patients Treated With Anakinra	Patients Treated With Prednisolone	Control Subjects	<i>P</i>
N	23	19	23	
Disease duration, y	11 (1–27)	10 (1–25)		0.9
DAS	5.1±0.9	5.3±1.1		0.9
Age, y	57±17	56±15	56±12	0.6
Body mass index, kg/m ²	29.3±7	28.2±7	28.4±2	0.6
Female sex, n (%)	17 (73)	14 (74)	17 (73)	0.9
Risk factors, n (%)				
Hypertension	11 (47)	8 (42)	9 (39)	0.4
Smoking	7 (30)	6 (31)	7 (30)	0.8
Dyslipidemia	7 (30)	5 (26)	5 (22)	0.4
Diabetes mellitus	5 (22)	4 (21)	4 (17)	0.6
Medication, n (%)				
ACE inhibitors	6 (27)	5 (21)	5 (25)	0.7
β-Blockers	3 (13)	2 (10)	2 (10)	0.7
Ca ²⁺ channel blockers	5 (22)	5 (26)	6 (27)	0.7
Diuretics	6 (27)	5 (26)	5 (25)	0.7
Statins	2 (9)	2 (10)	1 (8)	0.5
Antidiabetics	1 (8)	1 (5)	1 (8)	0.9

Values for disease duration are median and interquartile range. ACE indicates angiotensin-converting enzyme.

patients. We also measured malondialdehyde and nitrotyrosine as markers of nitrooxidative stress, ET-1 as a protein that affects vascular reactivity, and IL-6 and CRP as inflammatory markers.

Methods

Study Cohort

Acute Study

We examined 23 patients (mean age 57±17 years, 17 females) with RA (American Rheumatism Association criteria³¹) who had an inadequate response to disease-modifying antirheumatic drugs and corticosteroids and who were eligible to receive anakinra (Table 1). This group of patients participated in an acute, randomized, cross-over, and placebo-controlled trial with anakinra.

We used the following equation to calculate the composite disease activity score (DAS), which utilizes CRP, the visual analogue score (VAS) of well-being, and the number of tender and swollen joints (from a total of 28 joints assessed): DAS=√0.56×number of tender joints+√0.28×number of swollen joints+[0.70×ln(CRP)]+(0.014×VAS).³⁰ Changes in DAS are associated with improvement in physical activity.³²

Chronic Study

After completion of the acute study, the 23 patients with RA participated in a chronic, nonrandomized study with anakinra treatment (150 mg SC once daily) for 30 days. This group was compared with a group of 19 RA patients of similar age, sex, and DAS (Table 1) who also had an inadequate response to treatment with disease-modifying antirheumatic drugs and prednisolone and who were treated with an increase of their initial dose of prednisolone by 5 mg for 30 days.

None of the patients had cardiovascular or renal disease or ischemia during thallium scintigraphy or dobutamine stress. Patients with known or suspected coronary artery disease were excluded to ensure that measurement of CFR would reflect the status of coronary microcirculation and not the effects of epicardial coronary artery stenosis.

Twenty-three asymptomatic subjects of similar age and sex as the RA patients and with a normal ECG, echocardiogram, and treadmill test were selected as healthy control subjects among subjects attending the cardiology outpatient clinic. The study was approved by the hospital’s research committee, and all patients provided written informed consent.

Ultrasonography

All ultrasonography studies were performed with a Vivid 7 (GE Medical Systems, Horten, Norway) machine; they were digitally stored and analyzed by 2 observers (I.I. and I.P.) blinded to clinical and laboratory data and using a computerized station (Echopac GE, Horten, Norway). All patients and control subjects had adequate images for analysis.

Echocardiography

Aortic systolic (AoS) and diastolic (AoD) diameter were measured by 2D-guided M-mode echocardiography. Pulse pressure (PP) was simultaneously obtained by cuff sphygmomanometry. We calculated aortic strain as AS=100×(AoS–AoD)/AoD and aortic distensibility as AD=2×(AoS–AoD)/(AoD×PP)(cm²×dyn^(–1)×10^(–6)), as previously published.²⁹

Coronary flow velocities in the left anterior descending coronary artery were obtained with color-guided pulse-wave Doppler from long-axis apical projections with a 7-MHz transducer.²⁷ The maximal velocity (CF-Vmax) and velocity time integral (VTI) of the overall coronary flow wave (CF-VTI) and its diastolic component (CF-VTI_d) were measured at baseline and after adenosine infusion (140 μg · kg^(–1) · min^(–1)) for 3 minutes.²⁷ CFR was calculated as the ratio of hyperemic to resting CF-VTI_d.²⁷ Measurements from 3 cardiac cycles were averaged. Interobserver and intraobserver variabilities were calculated as the SD of the differences between the first and second measurements and expressed as a percentage of the average value. Interobserver and intraobserver variabilities of these measurements were 5% and 2%, respectively, as reported in previous studies.^{21,27}

Myocardial velocities were recorded with tissue Doppler imaging. The sample volume was placed in the septal, lateral, inferior, and anterior corners of the mitral annulus in the apical 4- and 2-chamber

views to record the systolic velocity (Sm), early diastolic velocity (Em), and late diastolic velocity (Am).²⁸ The mean value of the velocities at the 4 annular sites was used. The ratio of the mitral E wave measured by pulsed-wave Doppler to the Em was calculated as an index of LV diastolic filling pressures.²⁸ Interobserver and intraobserver variability of these measurements were 3% and 1.7%, respectively.

Endothelial Function

FMD and nitrate-induced vasodilation of the brachial artery were determined according to a previously published methodology.²⁶ Before the study, all subjects abstained from alcohol, caffeine, and food for 8 hours and ceased taking any vasoactive medications for 24 hours. Interobserver and intraobserver variabilities of the brachial artery diameter were 0.08 ± 0.19 and 0.1 ± 0.12 mm, and the day-to-day variability of FMD was $1.1 \pm 1\%$.²⁶

Pulse-Wave Velocity

PWV was measured with the Complior apparatus (Artech Medical, Pantin, France).³⁰ Waveforms were obtained over the right common carotid and the femoral artery.

Laboratory Assays

CRP was measured by high-sensitivity, particle-enhanced immunonephelometry (Dade Behring, Marburg, Germany; measurement range 0.175 to 1100 mg/L). Malondialdehyde was determined spectrophotometrically with a commercial kit (Oxford Biomedical Research [Rochester Hills, Mich] colorimetric assay for lipid peroxidation; measurement range 1 to 20 nmol/L). An ELISA was used to determine IL-6 (human high-sensitivity IL-6 ELISA, Diaclone, Stamford, Conn; assay sensitivity 0.8 pg/mL), nitrotyrosine (Hycult Biotechnology bv, Uden, Netherlands; measurement range 2 to 1500 nmol/L), and Et-1 (IBL Co, Ltd, Takasaki, Japan; measurement range 1.56 to 200 pg/mL).

Study Protocols

Acute Study

In 23 patients with RA, we used a double-blind, crossover, placebo-controlled protocol to study the effects of anakinra on biochemical, vascular, and LV function markers. All patients had baseline measurements of the examined markers. Measurement of PWV and echocardiography preceded the FMD study.

Patients were randomized to receive 1 subcutaneous injection of 150 mg of anakinra ($n=12$) or placebo ($n=11$). Assessment of the examined markers was repeated 3 hours after the injection, in accordance with the half-life of anakinra. Forty-eight hours after the first examination, patients were crossed over to the alternate treatment (placebo or anakinra), and measurement of the examined markers was repeated. The 48-hour interval between the 2 consecutive studies was chosen to ensure a sufficient washout period for anakinra in accordance with its half-life.²⁰

Chronic Study

During a chronic, nonrandomized study, 23 patients with RA who received anakinra (150 mg SC once daily) for 30 days were compared with 19 RA patients who received an increased dose of prednisolone for 30 days. Both groups had measurements of biochemical, vascular, and LV function markers at baseline and after 30 days of treatment. The healthy control subjects had a single baseline measurement of the examined markers.

Statistical Analysis

On the basis of $1 \pm 1\%$ (mean \pm SD)²⁶ and 5% variability²¹ for the measurement FMD and coronary flow velocities respectively, we assumed that a 25% change in vascular markers was clinically significant. In a previous study,²¹ the mean absolute change in CFR after intervention was -0.86 (range -1.36 to -0.37 ; 23% change). Thus, with a mean difference of 0.86, a variability of the difference of 1.36, an $\alpha=0.05$ (2-sided), and a power of 80%, the sample size

needed was calculated to be 23 patients for within-patient comparisons. In our previous studies,²⁶ the mean absolute change in FMD after intervention was 2.5%, and the variability of this change was 3%; thus, with an $\alpha=0.05$ (2-sided) and a power of 80%, the required sample size was calculated to be 13 patients.

Categorical data were compared among patients treated with anakinra or prednisolone and healthy control subjects by contingency tables (P value in Table 1) and between each treatment group and healthy control subjects by the χ^2 test or Fisher exact test when 5 or fewer patients were included in each cell (Table 1). Continuous variables were tested for normality with the Kolmogorov-Smirnov test. Normally distributed variables are given as mean \pm SD. Spearman correlation analysis was used to determine bivariate correlations. Because biomarkers had a nonnormal distribution, data are expressed as median (interquartile range) and were analyzed after transformation into ranks.¹⁷

ANOVA (general linear model, SPSS 13, SPSS Inc, Chicago, Ill) for repeated measurements was applied for the following comparisons: (1) in the acute study, for measurements of the examined markers at baseline, 3 hours after placebo, and 3 hours after anakinra; and (2) in the chronic study, for the effects of anakinra versus prednisolone, with measurements at baseline and 30 days after treatment used as a within-subject factor and type of treatment used as a between-subject factor. The F and P values of the interaction between time of measurement of the examined markers and type of treatment were calculated. The Greenhouse-Geisser correction was used when the sphericity assumption, as assessed by Mauchly's test, was not met. Post hoc comparisons were performed with Bonferroni correction.

The percent changes of the examined indices between baseline and after anakinra or between baseline and after placebo were compared with the Wilcoxon signed rank test (biomarkers) or paired t test (vascular and LV function markers). The percent changes of the examined indices between baseline and 30 days in the anakinra group versus changes in the prednisolone group were compared with the Mann-Whitney test (biomarkers) or unpaired t test (vascular and LV function markers). Comparisons between healthy control subjects and each treatment group at baseline or at 30 days were performed with unpaired t test (vascular and LV function indices) and Mann-Whitney test (biomarkers). Statistical significance was considered at $P < 0.05$.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient characteristic are shown in Table 1. Twenty patients complained of mild erythema at the injection site. None were withdrawn from the study because of adverse effects or inadequate response to treatment.

Acute Study

Biochemical Markers

Compared with baseline, the percent reduction in IL-6, malondialdehyde, nitrotyrosine, and ET-1 levels was greater after anakinra than after placebo (IL-6 $-29 \pm 3\%$ versus $0.9 \pm 1\%$, $P=0.003$; malondialdehyde $-25 \pm 5\%$ versus $9 \pm 3\%$, $P=0.03$; nitrotyrosine $-38 \pm 5\%$ versus $-11 \pm 3\%$, $P=0.001$; and ET-1 $-36 \pm 7\%$ versus $-11 \pm 3\%$, $P < 0.001$; Table 2). No changes were observed in CRP or lipid levels after treatment.

Vascular Function

Compared with baseline, FMD increased by $45 \pm 5\%$ after anakinra versus a decrease of $9 \pm 3\%$ after placebo ($P < 0.001$; Table 3). Nitrate-induced vasodilation remained unchanged ($P=0.2$). The percent increase in resting and hyperemic

Table 2. Acute Effects of Treatment With Placebo or Anakinra on Biomarkers

	Baseline	3 Hours After Placebo or Anakinra	P
3 Hours after placebo			
Cholesterol, mg/dL	212.1±46	209.9±40	0.8
LDL, mg/dL	132.1±40	130.9±38	0.7
HDL, mg/dL	66.1±18	66.8±19	0.8
Triglycerides, mg/dL	122.2±46	127.9±46	0.8
Malondialdehyde, nmol/L	2.2 (1.5–3.3)	2.4 (1.3–3.7)	0.8
Nitrotyrosine, nmol/L	787 (92–903)	707 (5.8–935)	0.2
IL-6, pg/mL	10.4 (8.2–16.7)	10.5 (7.1–16.7)	0.9
ET-1, pg/mL	2.8 (1.3–4.6)	2.5 (1.3–4.9)	0.9
CRP, mg/L	11.6 (6.5–35)	11.5 (5.8–35)	0.9
3 Hours after anakinra			
Cholesterol, mg/dL	212.1±46	211.7±46	0.9
LDL, mg/dL	132.1±40	132.4±40	0.8
HDL, mg/dL	66.1±18	65.9±18	0.8
Triglycerides, mg/dL	122.2±46	122.9±46	0.9
Malondialdehyde, nmol/L	2.2 (1.5–3.3)	1.7 (1.3–2.7)	0.03
Nitrotyrosine, nmol/L	787 (92–903)	488 (74–889)	0.004
IL-6, pg/mL	10.4 (8.2–16.7)	8 (5.7–9.2)	0.009
ET-1, pg/mL	2.8 (1.3–4.6)	1.8 (0.62–2.9)	<0.001
CRP, mg/L	11.6 (6.5–35)	11 (6.2–32)	0.9

P value refers to post hoc analysis (Bonferroni correction) by ANOVA for repeated measurements between baseline and those taken 3 hours after placebo or 3 hours after anakinra.

CF-Vmax, CF-VTI, and CF-VTI_d was greater after anakinra than after placebo (rest: 12±2% versus -3.8±3%, 13±3% versus 3.8±3%, and 11%±2 versus -8±6%, respectively; hyperemia: 27±2% versus 1.5±2%, 31±3% versus 2±2%, and 35±3% versus -0.4%±1, respectively; P<0.001 for all comparisons). CFR was increased by 29±2% after anakinra versus 4±2% after placebo (P<0.001).

The percent increase in aortic distensibility and strain was greater after anakinra than after placebo (45±7% versus 2±2% and 54±9% versus -4±3%, respectively; P<0.001 for all comparisons). Heart rate, systolic and diastolic blood pressure, pulse pressure, and PWV remained unchanged (P=0.1, P=0.41, P=0.44, P=0.9, and P=0.7, respectively).

LV Function

Compared with baseline, the Sm increased by 13±1% after anakinra versus a 1±0.9% decrease after placebo (P=0.001). E/Em was reduced by 15±1% after anakinra versus 7±1% after placebo (P=0.005; Table 3).

Chronic Treatment

The DAS was reduced from 5.1±0.9 to 3.4±0.9 after anakinra and from 5.3±1.1 to 4.1±0.9 after prednisolone (F for interaction=6.1, P=0.018; 34% versus 22% change, P=0.019).

Table 3. Acute Effects of Treatment With Placebo or Anakinra on Vascular and LV Function

	Baseline	3 Hours After Placebo or Anakinra	P
3 Hours after placebo			
FMD, %	5.3±3.0	4.8±2.7	0.9
NMD, %	20.3±7.9	20.2±6.4	0.2
PWV, m/s	9.4±2.8	9.3±2.4	0.9
Aortic distensibility, cm ² · dyne ⁻¹ · 0.10 ⁻⁶	1.56±1.1	1.61±1.5	0.9
Aortic strain, %	3.35±1.7	3.12±2.0	0.9
Rest CF-Vmax, cm/s	26±5	24±6	0.9
Rest CF-VTI _d , cm	9.2±1.4	8.4±1.6	0.7
Hyperemic CF-Vmax, cm/s	65±19	66±18	0.9
Hyperemic CF-VTI _d , cm	22.7±7.0	22.6±8.1	1
CFR _d	2.39±0.6	2.41±0.6	1
Sm, cm/s	8.4±2.1	8.3±1.5	0.9
Em/Am	0.83±0.4	0.85±0.5	0.7
E/Em	10.2±4.0	9.8±3.8	0.9
3 Hours after anakinra			
FMD, %	5.3±3.0	9.7±3.3	<0.001
NMD, %	20.3±7.9	21.5±7.1	0.1
PWV, m/s	9.4±2.8	9.5±2.7	0.7
Aortic distensibility, cm ² · dyne ⁻¹ · 0.10 ⁻⁶	1.56±1.1	3.41±1.8	0.001
Aortic strain, %	3.35±1.7	7.60±3.8	<0.001
Rest CF-Vmax, cm/s	26±5	29±6	0.01
Rest CF-VTI _d , cm	9.2±1.4	10.2±1.9	<0.001
Hyperemic CF-Vmax, cm/s	65±19	75±19	0.03
Hyperemic CF-VTI _d , cm	22.7±7.0	29.6±10	<0.001
CFR	2.39±0.6	2.85±0.7	<0.001
Sm, cm/s	8.4±2.1	9.5±2.4	0.02
Em/Am	0.83±0.4	0.88±0.4	0.04
E/Em	10.2±4.0	8.9±3.6	0.018

NMD indicates nitrate-mediated dilation; Em/Am, ratio of the early (Em) to the late (Am) diastolic wave of mitral annulus; and E/Em, ratio of the mitral E wave to the Em.

P value refers to post hoc analysis (Bonferroni correction) by ANOVA for repeated measurements between baseline and measurements taken 3 hours after placebo or 3 hours after anakinra.

Biochemical Markers

Compared with baseline, the percent reduction in IL-6, malondialdehyde, nitrotyrosine, CRP, and ET-1 was greater after anakinra than after prednisolone (IL-6 -61±8% versus -41±9%, P=0.02 malondialdehyde -33±2% versus 3±2%, P=0.006; nitrotyrosine -50±8% versus 0.5±1%, P=0.006; CRP -80±9% versus -58±6%, P=0.004; and ET-1 -40±7% versus -22±4%, P=0.04). There were no significant changes in lipid levels after treatment. Patients taking anakinra had higher baseline levels of biomarkers than healthy control subjects (malondialdehyde 2.2 [1.5 to 3.3] versus 1.3 [1.0 to 1.7] nmol/L; nitrotyrosine 787 [92 to 903] versus 0 [0 to 429] nmol/L; IL-6 10.4 [8.2 to 16.7] versus 1.1 [0.2 to 1.7] pg/mL; ET-1 2.8 [1.3 to 4.6] versus 1.0 [0.8 to

Table 4. Chronic Effects of Anakinra or Prednisolone on Biomarkers Versus Controls

	Anakinra (n=23)			Prednisolone (n=19)		
	Baseline	30 d	<i>P</i>	Baseline*	30 d	<i>P</i>
Cholesterol, mg/dL	212.1±46	211.9±46	0.9	210.2±40	214.9±39	0.9
LDL, mg/dL	132.1±40	129.3±40	0.86	131.1±38	135.2±36	0.2
HDL, mg/dL	66.1±18	67.9±17	0.9	66.9±19	64.2±21	0.7
Triglycerides, mg/dL	122.2±46	122.3±46	0.9	128.0±46	128.9±45	0.9
Malondialdehyde, nmol/L	2.2 (1.5–3.3)	1.5 (0.9–2.0)	0.013	2 (1.8–3.2)	1.9 (1.9–3.2)	0.54
Nitrotyrosine, nmol/L	787 (92–903)	388 (75–900)	0.005	787 (90–845)	743 (89–840)	0.9
IL-6, pg/mL	10.4 (8.2–16.7)	3.8 (2.9–7.1)	<0.001	9.7 (7.0–10.3)	5.3 (4.5–7.7)	0.03
ET-1, pg/mL	2.8 (1.3–4.6)	1.7 (0.8–2.5)	0.004	2.5 (1.3–3.6)	1.9 (1–3.1)	0.44
CRP, mg/L	11.6 (6.5–35)	2.7 (0.1–5.6)	<0.001	10.6 (6.4–38)	4.8 (1.8–8)	0.03

P value refers to comparisons between baseline and measurements made 1 month after treatment.

**P*=NS for comparisons between patients taking anakinra and patients taking prednisolone at baseline for all variables.

2.0) pg/mL; and CRP 11.6 [6.5 to 35] versus 1.4 [0.01 to 2.0] mg/L, *P*<0.05). Malondialdehyde, ET-1, and CRP levels became similar between patients and control subjects after treatment with anakinra. Conversely, patients treated with prednisolone had higher baseline and posttreatment levels of biomarkers than healthy control subjects (Table 4; *P*<0.05).

Vascular Function

Compared with baseline, the percent increase in FMD and CFR was greater after anakinra than after prednisolone (47±5% versus -14±6% and 35±5% versus -4±2%, respectively; *P*<0.001 for all comparisons; Table 5). The percent increase in all coronary flow indices was higher after anakinra than after prednisolone (*P*<0.05). Nitrate-induced vasodilation was similar between the 2 treatment groups (*F* for interaction=0.1, *P*=0.7). Aortic distensibility and strain showed a 3-fold increase after anakinra compared with a 7±3% and 11±3% increase after prednisolone (*P*<0.001 for all comparisons). The anakinra group had lower baseline

FMD, CFR, aortic distensibility, and aortic strain than healthy control subjects (FMD 5.3±3.0% versus 8.1±2.3%, *P*=0.004; CFR 2.39±0.6 versus 3.10±0.9, *P*<0.001; aortic distensibility 1.56±1.1 versus 3.71±1.1 cm²·dyne⁻¹·10⁻⁶, *P*<0.001; aortic strain 3.35±1.7% versus 8.12±2.3%, *P*<0.001). These indices became similar between patients and control subjects after treatment. Hyperemic CF-VTI and CF-VTI_d were lower in patients than in control subjects before anakinra treatment (29.1±8 versus 33.2±4 cm, *P*=0.04 and 22.7±7.0 versus 26.1±3.2 cm, *P*=0.02, respectively) and became higher in patients than in control subjects after treatment (43.1±10.1 cm, *P*=0.01 and 32.7±9.1 cm, *P*=0.004, respectively). Conversely, patients treated with prednisolone had lower FMD, CFR, aortic distensibility, and aortic strain than control subjects both before and after treatment (*P*<0.05). Hyperemic coronary flow markers were lower in patients than in control subjects before prednisolone treatment (*P*<0.05) and became similar between patients and control subjects after treatment.

Table 5. Chronic Effects of Anakinra or Prednisolone on Vascular and LV Function Versus Controls

	Anakinra (n=23)			Prednisolone (n=19)		
	Baseline	30 d	<i>P</i>	Baseline*	30 d	<i>P</i>
FMD, %	5.3±3.0	10.5±4.1	<0.001	5.0±1.9	4.3±1.6	0.25
NMD, %	20.3±7.9	22.3±6.3	0.2	20±8	19±5.4	0.8
PWW, m/s	9.4±2.8	9.5±2.9	0.7	9.8±1.8	9.6±2.6	0.7
AO distensibility, cm ² ·dyne ⁻¹ ·10 ⁻⁶	1.56±1.1	4.60±3.2	<0.001	1.3±0.9	1.4±0.9	0.45
AO strain, %	3.35±1.7	8.80±5.6	<0.001	2.70±1.2	3.11±1.5	0.5
Rest CF-Vmax, cm/s	26±5	31±6	0.001	25±6	28±8	0.09
Rest CF-VTI _d , cm	9.2±1.4	10.6±2.3	0.001	9.2±1.4	8.4±1.6	0.13
Hyperemic CF-Vmax, cm/s	65±19	77±22	0.045	67±20	74±28	0.19
Hyperemic CF-VTI _d , cm	22.7±7	32.7±9.1	<0.001	21.4±7	23.2±12	0.3
CFR	2.39±0.6	3.08±0.5	<0.001	2.50±0.6	2.41±0.5	0.19
Sm, cm/s	8.4±2.1	9.4±2.4	0.001	8.5±1.6	8.4±2.1	0.8
Em/Am	0.83±0.4	0.99±0.4	0.04	0.81±0.3	0.85±0.3	0.55
E/Em	10.2±4.0	8.1±2.0	<0.001	9.1±3.3	9.5±4.1	0.7

Abbreviations as in Table 3. *P* value refers to comparisons between baseline and measurements taken after 1 month.

**P*=NS for comparisons between patients taking anakinra and patients taking prednisolone at baseline for all variables.

LV Function

Compared with baseline, the percent improvement in Sm, Em/Am, and E/Em was greater after anakinra than after prednisolone ($20 \pm 2\%$ versus $1.1 \pm 1\%$, $P=0.001$; $19 \pm 2\%$ versus $5 \pm 1\%$, $P=0.04$; and $-21 \pm 2\%$ versus $4.4 \pm 2\%$, $P=0.005$, respectively). Both treatment groups had lower baseline Sm than control subjects (anakinra 8.4 ± 2.1 cm/s and prednisolone 8.5 ± 1.6 cm/s versus control subjects 9.3 ± 1.6 cm/s, $P=0.028$ and $P=0.03$, respectively). After treatment, the anakinra group had similar Sm as control subjects ($P=0.9$), whereas the prednisolone group had lower Sm than control subjects ($P=0.03$). Em/Am and E/Em remained higher in patients (Table 5) than in control subjects (Em/Am 1.6 ± 0.6 and E/Em 6 ± 1.1) throughout the study ($P < 0.05$).

Interrelation of Changes After Treatment

The percent increase in CFR was related to the reduction in nitrotyrosine and malondialdehyde 3 hours ($r_s=0.50$, $P=0.01$ and $r_s=0.49$, $P=0.02$, respectively) and 30 days ($r_s=0.53$, $P=0.005$ and $r_s=0.50$, $P=0.01$, respectively) after anakinra. Modest correlations were observed between the changes in CFR, IL-6, and ET-1 after anakinra ($P < 0.05$).

The percent increase in FMD was equally related to the reduction of malondialdehyde, nitrotyrosine, and ET-1 at 3 hours and 30 days after anakinra ($P < 0.05$). The percent increase in aortic distensibility 3 hours and 30 days after anakinra was related to the reduction in malondialdehyde ($r_s=0.63$, $P=0.001$ and $r_s=0.55$, $P=0.004$), nitrotyrosine ($r_s=0.52$, $P=0.009$ and $r_s=0.50$, $P=0.01$), IL-6 ($r_s=0.62$, $P=0.002$ and $r_s=0.60$, $P=0.004$), and ET-1 ($r_s=0.50$, $P=0.01$ and $r_s=0.49$, $P=0.02$). Similar associations were observed for aortic strain ($P < 0.05$). Both the percent increase in Sm and the reduction in E/Em were related to the reduction in IL-6 and nitrotyrosine at 3 hours ($P < 0.001$) and 30 days ($P < 0.001$) after anakinra. The percent increase in FMD was related to the increase in resting and hyperemic CF-VTid, CFR ($P < 0.05$), aortic strain, and aortic distensibility ($P < 0.05$) after anakinra.

Discussion

In an acute, double-blind, crossover, placebo-controlled trial of patients with RA, we have shown that administration of IL-1ra (anakinra) caused a greater reduction of nitrooxidative stress, IL-6, and ET-1 than placebo. After acute anakinra administration, changes in biomarkers were associated with a parallel improvement in vascular and LV function. After 30 days of treatment, the improvement in biomarkers and vascular and LV function was greater in patients treated with anakinra than in patients treated with prednisolone.

Acute Study

Effects of IL-1 Inhibition on Vascular Function

Adenosine-induced CFR is thought to be endothelium dependent.^{21–23} IL-1 may cause endothelial dysfunction and, consequently, an impaired CFR through increased nitrooxidative stress^{9,10} and release of ET-1.^{8,14} Reduction of nitrooxidative stress rapidly restores endothelium-dependent relaxation of rat aorta¹² and coronary vasomotor function.³³

In an acute, double-blind trial, we have shown that an IL-1ra reduced ET-1, IL-6, malondialdehyde, and nitrotyrosine after 3 hours of treatment compared with placebo. Furthermore, we demonstrated a parallel improvement in FMD, resting and hyperemic coronary flow, CFR, aortic distensibility, and aortic strain after anakinra treatment. Of all biomarkers, the reduction in nitrotyrosine and malondialdehyde demonstrated the highest correlation with improvement of endothelial, coronary, and aortic function.

Experimental studies have shown that IL1ra (1) reduced oxidative burst as assessed by peroxynitrite by 2 hours³⁴; (2) completely abolished inflammation, oxidative stress, and the resultant tissue damage¹⁸ when given 30 minutes before and 3 hours after the induction of oxidative lung injury; and (3) diminished the effects of IL-1–induced free radical production on fibrinolysis within 1 hour and thus improved endothelial function in microvessels.³⁵ Therefore, studies suggest a rapid effect of IL-1ra on oxidative stress that leads to an early improvement in microcirculation and vascular function.³⁵ Antioxidant treatment has been shown to improve FMD and CFR within 3 hours^{22,23,25} in humans. Therefore, in the present study, the acute beneficial effects of IL-1 inhibition on vascular function may be related to the concomitant reduction in nitrooxidative stress.

In the present study, the reduction in circulating ET-1 after anakinra was also related to the improvement in FMD and CFR. Thus, the acute reduction of ET-1 by anakinra may also have contributed to the rapid improvement in vascular function.

IL1ra reversed the effects of IL-1 on aortic function in rats within 5 hours³⁶ through inhibition of nuclear factor- κ B and subsequent reduction of inducible nitric oxide synthase production, blocked IL-1–mediated activation of the nuclear factor- κ B within 5 minutes,³⁷ and reduced IL-1–induced IL-6 production within 2 hours after stimulation³⁷ through inhibition of nuclear factor- κ B. Thus, a rapid inhibition of nuclear factor- κ B by anakinra may explain the association between the improved aortic function and reduction in IL-6 in the acute phase of the present study.

Increased nitrooxidative stress mediates a depressed endothelium-dependent relaxation of aorta in experimental models of RA.¹² Nitric oxide and/or endothelin regulates local arterial distensibility in vivo.^{7,24} In the present study, the acute reduction in malondialdehyde, nitrotyrosine, and ET-1 by anakinra, was related to improved aortic function. This finding suggests that the combined reduction in nitrooxidative stress and endothelin after IL-1 inhibition may have caused the early improvement in aortic function. The lack of a significant effect of anakinra treatment on PWV suggests either that a single dose of anakinra was not sufficient to restore function along the entire length of the thoracic-abdominal aorta or that the present study did not have sufficient power to detect subtle changes in PWV. The ascending aorta is a more elastic vessel than the abdominal aorta and its branches. Thus, the aortic root may respond more rapidly than the more rigid abdominal aorta to changes in oxidative stress, nitric oxide, and endothelin levels that lead to concomitant changes of its distensibility.³⁸

A large study of patients with RA and comorbidities including coronary artery disease¹⁹ has shown that there were no differences in cardiovascular events or serious infections after anakinra compared with placebo. Thus, anakinra has a more favorable safety profile than other humoral regimens that improve endothelial function.³⁹

Effects of IL-1 Inhibition on LV Function

IL-1 activity may cause reversible myocardial dysfunction through production of peroxynitrate and IL-6.^{11,15–17} In the present study, the reduction in IL-6 and nitrotyrosine was related to an acute improvement in LV function after anakinra. This association is in line with studies demonstrating that IL-1ra rapidly inhibits IL-6 production and reduces peroxynitrate^{18,34–37} and that the IL-6-mediated negative inotropic effect is completely reversed by 40 minutes after removal of this cytokine in vitro.^{16,17} Additionally, the significant improvement in CFR and aortic function may have contributed to the improvement in LV performance after anakinra.

Chronic Study

In the present study, the improvement in biomarkers and vascular and LV function was greater in the anakinra group than in the prednisolone group after 30 days of treatment. The acute beneficial effects of anakinra on nitrooxidative stress and vascular and LV function were maintained after chronic treatment compared with the conventional antiinflammatory regimens. Compared with healthy control subjects, both treatment groups had abnormal baseline biomarkers and vascular and LV function; however, malondialdehyde, ET-1, CRP, CFR, FMD, aortic function, and Sm became similar between patients and healthy control subjects after anakinra but not after prednisolone treatment. This finding suggests that the effects of IL-1 inhibition on oxidative stress and inflammation may lead to normalization of vascular function.

Study Limitations

The study design does not enable exploration of causality for the changes in vascular and LV function after anakinra treatment. Although the acute study timings were based on the pharmacokinetics of anakinra,²⁰ there may have been a carryover effect in the crossover phase. However, the persistent effects of anakinra compared with prednisolone in the chronic study, in which no carryover effects occur, support the significant effects of anakinra on vascular and LV function. Because RA patients with coronary artery disease were excluded, the effects of anakinra in the presence of coronary artery disease were not explored in the present study. The large number of comparisons in the present study may have caused a type I error. Improved physical activity after anakinra as reflected by the reduced DAS³² may have contributed to the improvement in biochemical, vascular, and LV parameters. The noninvasive assessment of vascular and LV function should also be acknowledged as a limitation.^{26–30}

Conclusions

In the present study, we have shown that administration of a commercially available IL-1ra improves vascular and LV

function and is related to a concomitant reduction in nitrooxidative stress and ET-1 levels in patients with RA.

Disclosures

None.

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CLINICAL PERSPECTIVE

Atherogenesis shares similar pathophysiological mechanisms with the inflammatory process in patients with rheumatoid arthritis, including increased nitrooxidative stress and release of proinflammatory cytokines and endothelins. Interleukin-1 mediates atherogenesis and coronary vasoreactivity. Anakinra, a human recombinant interleukin-1a receptor antagonist, is currently used for the treatment of rheumatoid arthritis. In the present study, we have shown that treatment with anakinra improves coronary flow and endothelial, arterial, and left ventricular function compared with placebo and is related to a concomitant reduction of nitrooxidative stress, inflammation, and endothelin in patients with rheumatoid arthritis. Additionally, anakinra was more effective than corticosteroids in improving vascular and left ventricular function after 30 days of treatment. In a large study of patients with rheumatoid arthritis and comorbidities, including coronary artery disease, there were no differences in cardiovascular events or serious infections after anakinra compared with placebo. Anakinra has a more favorable safety profile than other humoral regimens that improve vascular function. Thus, inhibition of interleukin-1 activity may improve outcome by improving vascular and left ventricular function in patients with rheumatoid arthritis and may be a potential therapeutic target in patients with coronary artery disease.